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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,932	05/30/2001	Lijun Wu	MPI96-027CP2RCE2M	9497

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/870,932	WU ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *158,160-163,166,179,181-184,187,200,202-205 and 208* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *158,160-163,166,179,181-184,187,200,202-205 and 208* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 16 May 2088 have been entered. Claims 158, 160 – 163, 166, 179, 181 – 184, 187, 200, 202 – 205, and 208 are pending and under examination.

Priority

2. The effective filing date of all pending claims is 11 July 1997 as set forth in the previous office actions. Applicant did not traverse the examiner's determination of priority.

Withdrawn Rejections and Objections

3. The following rejections and objections set forth in the previous office action are withdrawn:

A. The rejection under 35 USC 112, first paragraph for lack of adequate written description is withdrawn in light of the amendments to claim 200 which cancel the subject matter the examiner had considered not to be fully described.

B. The rejection under 35 USC 102(a) over Bleul is withdrawn in light of the arguments. Applicant persuasively argues that the 5C7 antibody disclosed by Bleul does not bind to the second extracellular loop of CCR5as recited in the claims. Applicant points to evidence from the specification which indicates that the antibody binds to a different region of the receptor.

C. The rejections under 35 USC 103(a) as obvious over Bleul in view of Hoxie, and further in view of Rodwell or Osband are withdrawn. As explained above, the specification provides evidence that the 5C7 antibody of Bleul does not bind to the second extracellular loop of CCR5. The remaining references fail to cure this deficiency, so the rejections under 35 USC 103 are withdrawn.

E. The non-statutory double-patenting rejection is withdrawn. The terminal disclaimer filed on 16 May 2008 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent 6,528,625 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Maintained Rejections

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 158, 160 – 163, 166, 179, 181 – 184, 187, 200, 202 – 205, and 208 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Li (U.S. Patent 6,025,154) in view of Li (U.S. Patent 6,759,519), Rapport (1996. Journal of Biological Chemistry 271:17161 – 17166), Combadiere (1996. Journal of Leukocyte Biology 60: 147 – 152), Samson (1996. Biochemistry 35:3362 – 3367), and Atchison (1996. Science 274:1924 – 1926), as evidenced by Wu (1997. Journal of Experimental Medicine 186:1373-1381) and Samson (1997. Journal of Biological Chemistry 272:24934 – 24941).

This rejection is maintained for the reasons previously made of record and explained in further detail herein. Note that the ‘154 and ‘519 patents to Li are cumulative, reference herein is to the ‘154 patent unless otherwise noted. The reasons why each claim limitation are met by the prior art references have been set forth previously, and for the sake of brevity will not be repeated here. Rather the teachings of the references are summarized and the arguments filed 16 May 2008 will be addressed.

Briefly, Li teaches antibodies to a protein called human HDGNR10, which is the same as human CCR5. Li also teaches antibodies that bind to the extracellular region (see ‘519 patent, for example claims 1 and 11) and also teaches that the inhibitors of the invention, which of course include antibodies, are those that inhibit binding of chemokine ligands (see Li ‘154 patent, column 12 lines 1 – 28). However Li does not explicitly teach selection of the second extracellular domain as the ligand binding region, does not teach that the antibodies inhibit binding of the specific ligands MIP-1□, MIP-1□, or RANTES, or inhibit HIV infection, as recited in independent claims 158, 179, and 200.

Samson (1996), Combadiere (1996), and Raport (1996) each teach binding of ligands to CCR5 and teaches that binding activates the receptor. See for example Combadiere for identification of MIP-1□, MIP-1□, and RANTES as agonists of the CCR5 (also called CC CKR5), Samson 1996 for identification of these ligands, and Raport, abstract as well as pp. 17165 – 17166. Both Raport (p. 17166) and Combadiere (p. 151) teach that these ligands are known to suppress HIV-1 entry into cells, and indicate that CCR5 is the strongest candidate for a chemokine HIV receptor. However none of the references explicitly teaches making antibodies that both inhibit ligand binding and HIV entry as recited in claims 158, 179, and 200.

Atchison teaches that the second extracellular domain of CCR5 contains is sufficient for HIV-1 entry into cells. Additionally, Atchison provides several examples of proteins which contain the second extracellular loop of CCR5 that also allow for HIV-1 entry. See for example Figure 3; note that "2555", which has the N-terminus of CCR2 (residues 1-44) fused to the remainder of CCR5 (residues 33 – 352) allows for HIV-1 entry (see also footnote 12). While not every chimeric protein containing the second extracellular loop allows for HIV-1 entry, the reference by Atchison clearly directs the artisan of ordinary skill to the second extracellular loop as one of a very few regions which acts as an HIV coreceptor activity. Atchison also teaches which regions of CCR5 are responsible for ligand binding and signaling (see Figure 4 for example). However Atchison does not teach antibodies.

It would have been obvious to one of ordinary skill in the art to modify the methods of Li, who teaches making antibodies against the extracellular domains of CCR5 and selecting those that inhibit ligand binding, to select those that inhibit binding of MIP-1□, MIP-1□, or RANTES and HIV entry, with a reasonable expectation of success. The motivation to do so would be to make an antibody that can inhibit HIV entry, which could be useful as an therapeutic for HIV.

Applicant argues, in the remarks filed 16 May 2008, that the invention as claimed would not have been obvious to one of ordinary skill in the art in view of the prior art cited by the examiner. Applicant makes several arguments, each of which will be addressed in turn, Including an argument that certain references teach away from the invention, that there would not have been a reasonable expectation of success, and that the examiner has improperly relied on hindsight reasoning in coming up with his determination of obviousness.

Applicant's arguments have been fully considered but they are not persuasive. On p. 11 of the remarks filed 16 May 2008, applicant argues that Atchison teaches away from the second extracellular loop as the locus of HIV entry. Atchison acknowledges that the CCR5 receptor is

an HIV coreceptor (p. 1924 first paragraph) and presents the results from two series of experiments designed to determine which parts of the receptor are crucial for it to act as a coreceptor of HIV. At pp. 1924 – 5, Atchison discusses the results of experiments in which chimeric receptors between human CCR5 (which binds HIV) and mouse CCR5 (which does not bind HIV) were made. At p. 1924 3rd column Atchison teaches that a chimera containing the mouse N-terminal extracellular region fused to the remaining components of the human receptor allows HIV entry, suggesting that an HIV entry point is contained within the human membrane-spanning regions, the intracellular loops, or the extracellular loops. Atchison teaches that each of extracellular loops 1, 2, and 3 all allow for HIV coreceptor activity (p. 1924, third column, first complete paragraph). Additionally, Atchison presents data indicating that a fusion protein wherein the N-terminal extracellular region of CCR2 (which does not act as an HIV coreceptor) is fused to the remaining part of the CCR5 receptor (which of course does act as an HIV coreceptor), including the second extracellular loop, has robust HIV coreceptor activity. See Figure 3, compare bar for 5555 (human CCR5) with 2555. Atchison concludes that "rather than a single site of interaction between HIV-1 and the coreceptor, multiple elements distributed throughout the extracellular segments appear to contribute to viral entry." This is not a teaching away from the importance of the second extracellular loop, but rather indicates that this loop is one of a few regions to be targeted in order to inhibit HIV entry. The reference by Atchison, taken as a whole, indicates that the second extracellular loop is one of a limited number of regions to be targeted in order to decrease HIV binding to this receptor.

At p. 12 of the remarks, applicant argues that Rucker (Cell 87:437-446, 1996) teaches away from the claimed invention. The examiner has closely reviewed the reference by Rucker and has concluded that it does not in fact teach away from the importance of the second extracellular loop in allowing for HIV entry. While the reference by Rucker concentrates on the role of the N-terminus of CCR5 in allowing HIV entry, the reference teaches that this is not the only region of this receptor responsible for entry. At p. 439 second column first complete paragraph, Rucker states that "we found that no single extracellular domain of CCR5 is required for cofactor function when replaced with the homologous domain from the CCR2b receptor... That [the amino terminal domain, which had been shown to be sufficient for HIV entry] is not absolutely required for cofactor function indicates that one or more additional domains of CCR5 play an important role in virus entry and membrane fusion." Additionally, Rucker teaches that chimera 25-13, which has the N-terminal region and second extracellular loop from CCR5,

allows for HIV entry. See p. 441 Figure 5A which indicates the structure of 25-13 (light gray shading indicates CCR2b regions, black indicates CCR5 regions), Figure 5B which indicates entry of HIV is the same in CCR5-containing and 25-13-containing cells, and p. 443 last complete paragraph. Rucker concludes that the interactions between HIV and its coreceptors (such as CCR5) are “conformationally complex” (abstract). Taken together with the teachings of Atchison, who indicates that there are multiple regions of interaction between the virus and the receptor, the reference by Rucker indicates that each of the extracellular loops is important for viral entry. Thus it does not teach away from the claimed invention. As Rucker (p. 437 second column first complete paragraph), Raport (p. 17166), and Combadiere (p. 151) all teach that known ligands of CCR5 suppress HIV-1 entry into cells, and the references by Atchison and by Rucker point to the second extracellular loop as one of a small number of regions that are important for HIV entry, the artisan of ordinary skill would have been specifically guided to make antibodies that bind to this region that inhibit both ligand binding and HIV entry, as claimed. The artisan could use the screening assays described by Li to find the relevant antibodies.

Applicant also argues, beginning at the end of p. 12 of the remarks, that the artisan of ordinary skill would not have had a reasonable expectation of success in making the claimed invention. Applicant argues that “one of skill in the art at the time, reading that chemokine ligands of CCR5 block HIV infection, would not necessarily expect that antibodies that block access of those chemokines to CCR5 to help block HIV.” The examiner disagrees with this conclusion. Clearly, it is uncontested that at the time the invention was made it was known that ligands to CCR5 block HIV. The most parsimonious explanation for this is that they occupy an important HIV entry site. Antibodies raised against this site, i.e. the second extracellular loop, would of course block ligand binding, and since they physically occupy the same site as those ligands which block HIV entry, the antibodies would also be expected to block HIV entry.

At p. 13 of the remarks, applicant argues that by citing Wu 1997 (IDS reference AS4), the examiner is improperly relying on hindsight in determining obviousness. The examiner did not cite the reference as providing a reason to make the invention now claimed, but rather to indicate that it would have been reasonable to expect success. At the end of p. 13, applicant argues that the post-filing reference by Roscкhe provides evidence that not all antibodies against CCR5 that block ligand binding also inhibit HIV infection, and according to applicant indicates that one of ordinary skill in the art would not "inevitably succeed in generating antibodies that <u>also</u> block HIV infection" (emphasis in original). The examiner has not made an

argument that all antibodies that block chemokine binding inherently have the HIV-blocking property. Additionally, it is noted that the standard to be used in determining obviousness is not absolute guarantee of success, but rather "a reasonable expectation of success"; see MPEP § 2143.02(I).

For the reasons explained above, the invention as claimed would have been obvious to one of ordinary skill in the art, at the time the invention was made. It is believed that all relevant arguments have been addressed.

New Rejections

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 158, 160 – 163, 166, 179, 181 – 184, 187, 200, 202 – 205, and 208 are rejected under 35 U.S.C. 102(e) as being anticipated by Combadiere (U.S. Patent Application Publication 2003/0195348, published 16 October 2003, filed 15 May 2003, claiming benefit of an earlier-filed non-provisional application on 28 May 1997 and an earlier-filed provisional application on 28 May 1996). Applicant is reminded that the effective filing date of all pending claims is 11 July 1997.

Combadiere teaches antibodies that bind to the human CCR5 receptor. See for example p. 1 paragraph [0009] and p. 2 paragraph [0014], which discusses the CCR5 receptor and antibodies thereto, and specifically teaches that antibodies and other blocking agents inhibit HIV fusion. At paragraph [0023], Combadiere teaches that RANTES, MIP-1α, and MIP-1β are agonists (i.e., ligands which activate) CCR5.

On pp. 7 - 9, Combadiere discusses the antibodies to CCR5 in more detail. At paragraphs [0067] – [0069], the reference teaches that the antibodies that bind CCR5 block HIV entry into human cells, and teaches that the antibodies are raised against any of the three extracellular loops of the receptor. These are referred to by Combadiere as SEQ ID NO:5 – 7;

see paragraphs [0069] and [0089], as well as Figure 2, which shows the three extracellular loops of the receptor. At paragraph [0069] Combadiere teaches that their antibodies not only block HIV entry but also block binding of chemokines, i.e. the known ligands of the CCR5 receptor. Note particularly first sentence of this paragraph, which lists both of these as properties of the antibodies, and final sentence of this paragraph, which states that the antibodies can have any or all of the recited functions. As the reference teaches raising antibodies against the second extracellular loop of CCR5, and teaches that the antibodies block both HIV entry and ligand binding, it anticipates claim 158.

Claims 160 – 163 are anticipated as Combadiere teaches monoclonal antibodies (paragraph [0072]), chimeric and specifically humanized antibodies (paragraph [0075]), and human antibodies (paragraphs [0075] – [0076]), as well as binding fragments thereof. Claim 166 is anticipated as the reference teaches how to obtain several of the cited fragments, for example at paragraph [0078]. Claims 179, 181 – 184, and 187 are anticipated as Combadiere teaches compositions comprising the antibodies and physiologically acceptable carriers; see for example paragraph [0111]. Claims 200, 202 – 205, and 208 are anticipated as they require nothing other than the antibodies themselves.

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker, Ph.D./
Patent Examiner, Art Unit 1649
August 15, 2008